SOMATIC AND COGNITIVE MARKERS IN SCHIZOPHRENIA

Ph.D. Thesis

András Sándor Hajnal, MD

University of Pécs
Medical School
Department of Psychiatry and Psychotherapy

Clinical Neuroscience Doctoral School (D221)
Head of Doctoral School: Prof. Dr. Sámuel Komoly, MD, DSc
Psychiatry Programme (B-1/2012)
Head of Programme: Prof. Dr. Tamás Tényi, MD, PhD
Thesis supervisor: Prof. Dr. Tamás Tényi, MD, PhD

Pécs, 2016.

Table of contents

List of abbreviations

aIPS - anterior intraparietal sulcus

BA - Brodmann area

DMN - default mode network

DMPFC - dorsomedial prefrontal cortex

DLPFC - dorsolateral prefrontal cortex

IPL - inferior parietal lobe

MFG - middle frontal gyrus

MPA - minor physical anomaly

MTG - middle temporal gyrus

PFC - prefrontal cortex

SFG - superior frontal gyrus

STG - superior temporal gyrus

STS - superior temporal sulcus

ToM - theory of mind

I. Examination of markers in relatives of patients with schizophrenia

Introduction

Among the several theories about the origin and background of schizophrenia the impairment of neurodevelopment may be the most dominant. (Buckley, 1998; Tandon et al.; 2008, Tényi and Trixler, 1999; Weinberger et al., 1987).

This is supported by the typical beginning in adolescent or young adult age, several and well documented structural and functional abnormalities at the onset of the illness (Buckley, 1998; Johnstone et al, 1976; Tandon et al., 2008), the premorbidly existing mild, but measurable intellectual deficits (Tandon et al., 2008), and the neuropathological findings supporting the developmental rather than acquired encephalopathy (Falkai et al., 1999).

According to the neurodevelopmental theory of schizophrenia – which is based on the findings mentioned above - a prenatal, static non-progressive anomaly in brain-development interacts with the normal the normal developmental process (Weinberger et al., 1987), so the so-called pre-schizophrenic traits found premorbidly in some of the patients, and the different psychotic symptoms developed later can be originated from these neurodevelopmental deficits.

Minor physical anomalies as the markers of neurodevelopment in schizophrenia

Minor physical anomalies (MPAs) are insignificant errors of morphogenesis which have a prenatal origin and may bear major informational value. The presence of minor physical anomalies is a sensitive physical indicator of embryonic development. Since both the central nervous system and the skin are derived from the same ectodermal tissue in utero, minor physical anomalies may be external markers of abnormal brain development. Minor physical anomalies are considered to develop during the first and/or early second trimester of gestation (Pinsky, 1985; Méhes 1988; Tényi et al., 2004, 2009) and represent potentially valuable indices of disturbances in early neurodevelopment. Once formed they persist into adult life and are readily detected on visual examination of the particular body area. Their more frequent presence is well documented in several illnesses with neurodevelopmental origins. In addition a number of studies (Méhes, 1988; Tényi és Trixler, 1999) have shown a higher prevalence of MPA-s in patient with schizophrenia, compared to the healthy population.

Endophenotype studies in schizophrenia

Endophenotypes are intermediate phenotypes that fill the gap between genes and diseases, They can be objectively measured and sharply differentiated from psychiatric symptoms, thus helping the biological and genetic research of the etiology of these illnesses. According to Gottesman and Gould (2003) endophenotypes should be: (1) associated with the illness, (2) heritable, (3) state-independent, (4) found in unaffected relatives at a higher rate than in the general population, and (5) shown to co-segregate with the illness within families.

Later Gottesman extended the definition with objective, reliable measurability and specificity, as a sixth criterion. Different possible endophenotypes have been identified in schizophrenia: specific cognitive deficits (Snitz et al., 2006), and the so-called neurological soft signs (Chan and Gottesman, 2008), the occurrence of which has been studied among patients with schizophrenia, healthy relatives of schizophrenia patients, and healthy control patients. Minor physical anomalies (MPAs) are suggested as potential endophenotypes on account of the findings that MPA-s are clearly state-independent trait-markers, and according to a number of studies MPA-s are more common in schizophrenia patients than in healthy controls (Weinberg et al., 2007; Xu et al., 2011).

Several studies examined the prevalence of MPA-s in healthy first-degree relatives of patients with schizophrenia, with variable outcomes. These contradictions may be associated with the problems in the use of the Waldrop-scale (and it's modified versions - Lane-scale, Gourion-scale) for the detection of these signs. The Waldrop-scale contains only 18 minor physical anomalies (Waldrop, Goering, 1971) while in recent paediatric literature more than 50 anomalies have been listed. (Pinsky,1985; Méhes, 1988). Another basic problem with the Waldrop-scale that it makes no distinction between minor malformations, which arise during organogenesis and phenogenetic variants, which appear after organogenesis (Pinsky, 1985; Méhes, 1988; Trixler, Tényi, 2000). Minor malformations are always abnormal and are qualitative defects of embryogenesis. In contrast phenogenetic variants are quantitative defects of final morphogenesis and arise after organogenesis.

Aims of the study

The aim of the present study was to investigate the rate and topological profile of minor physical anomalies - using the Méhes Scale to differentiate minor malformations and phenogenetic variants - in the relatives of patients with schizophrenia comparing them to normal control subjects. The following hypotheses have been tested: (1) Minor physical anomalies are more common in the relatives of schizophrenia patients compared to normal controls, which promotes the hypothesis, that MPAs can be endophenotypic markers of schizophrenia, (2) a higher rate of minor physical anomalies is found predominantly in the head and facial regions among the relatives of schizophrenia patients, pointing at aberrant early (first and second trimester) brain development.

Material and methods

Study subjects

Using a list of 57 minor physical anomalies collected by Méhes (1988), 20 first-degree unaffected relatives of patients with the diagnosis of schizophrenia were examined. 11 parents and 9 siblings were included in the study, the mean age of the relatives was 58.6±6.2 years. Only four relatives were at the at-risk age for schizophrenia (2 relatives at the age of 36 and 2 relatives at the age of 41), all the other relatives age was 53 years or more. As a comparison 20 normal control subjects matched for sex, age and ethnic origin were also observed for minor physical anomalies. Controls were excluded if they endorsed any personal or family history (in the first- or second-degree relatives) of psychotic disorders, mood disorders and schizotypal personality disorder. First-degree relatives of schizophrenia patients were excluded if they endorsed a personal history of psychotic disorders, mood disorders or schizotypal personality disorder. For all participants, psychotic disorders, mood disorders and schizotypal personality disorder were ruled out independently by two experienced psychiatrists according to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 2000). All available clinical information and data were obtained from structured clinical interviews.

Examination of minor physical anomalies

We have used the Méhes Scale for evaluation of minor physical anomalies, which includes 57 minor signs (Trixler et al., 1997; 2001; Tényi et al., 2009). Minor physical anomalies are connected to body regions for comparison and analysis of data. A clear differentiation between minor malformations and phenogenetic variants were introduced, the scale and detailed definitions were published earlier (Trixler et al., 2001). All participants gave informed consent, the study was performed in accordance with the Declaration of Helsinki and was evaluated following institutional guidelines. The examination of minor physical anomalies was done qualitatively (present or absent) without scores being used, but where it was possible, measurements were taken with callipers and tape to improve the objectivity of examination.

Statistical analysis

Before the statistical analyses interrater reliability was tested and the kappa coefficient was > 0,75 for all items. Statistical analyses were carried out by applying the Mann - Whitney U-test for and the chi-squared test for the comparison of the two groups with each other. 2-sided Fisher's exact tests were used to compare the two groups with each other by body regions, the level of significance chosen was $p<0,05$. For the analysis of the frequency of each individual minor physical anomaly the two-sided Fisher's exact probability test was used, the level of significance chosen was $p<0,05$. All the statistical analyses were done by the use of SPSS Version 21.

Results

The comparison of two groups with the Mann-Whitney-U-test showed significant differences between them (relatives of schizophrenia patients: mean rank: 25.85 versus normal controls: mean rank: 15.15, $p=0.003$.). The differences of the MPA profiles between the two groups are shown on Table 1.

Table 1.

	0 MPA	1 MPA	2 MPAs	3 MPAs	4 MPAs
Controls (no.20)	11	7	2	0	0
Relatives (no.20)	5	3	4	4	4

As in our previous studies (Trixler et al., 2001; Tényi et al., 2004) we evaluated a dichotomization by establishing two groups: (1) none or only 1 MPA, (2) MPAs more than 1. While in the control group the number of individuals with none or only with 1 MPA was 18 (90%), in the relative group it was 8 (40%), the chi-squared test showed a statistically significant difference (p=0.001). The significantly different between group data of the 2-sided Fisher's exact test comparisons of percentages according to body regions are shown on Table 2.

Table 2.

	Ear region	**Head region**	**Mouth region**	**Eye region**	**Trunk region**	**Hand region**	**Feet region**
Controls (no.20)	0,00%	10,00%	0,00%	0,00%	25,00%	10,00%	10,00%
Relatives (no.20)	20,00%	40,00%	30,00%	10,00%	40,00%	35,00%	10,00%
Fisher exact test, level of significance	p=0,053 ns	p=0,032 significant	p=0,010 significant	p=0,244 ns	p=0,250 ns	p=0,064 ns	p=0,698 ns

Relatives of schizophrenia patients showed a higher frequency of MPAs in the head and the mouth regions compared to normal control subjects. By the differentiation of minor malformations and phenogenetic variants, we have found that phenogenetic variants were more common in the relatives of schizophrenia patients compared to the control group (relatives: mean rank: 24.70,versus controls: mean rank: 16.30, P=0.023), while minor malformations were not more prevalent in the relative group, although a strong tendency toward a more common appearance could be detected (relatives: mean rank : 24.08, controls: mean rank: 16.92, p=0.052, NS). Comparing phenogenetic variants and minor malformations by body regions, between the two groups phenogenetic variants in the mouth region were more prevalent (Fisher's exact test, two-sided: 0.047) in the relatives of schizophrenia patients. The results of comparisons of individual MPAs among the two groups are shown on

Table 3. Only one minor malformation (flat forehead) was more prevalent (p=0.044) in the schizophrenia relatives group compared to the normal control group.

Table 3.

	Relatives, number of individuals	Controls, number of individuals	Fisher's exact-test, two-sided
Flat forehead	7	1	p=0,044 significant

Discussion

Since the available evidence indicates that minor physical anomalies arise through processes which act during the early stages of embryonic and foetal life, our results on the overrepresentation of these anomalies in the relatives of schizophrenia patients promotes the hypothesis, that MPAs can be endophenotypic markers of schizophrenia. We report here, that minor physical anomalies were more common in the head and mouth regions among the relatives of schizophrenia patients compared to normal controls and the individual analyses showed that one minor malformation (flat forehead) was also more prevalent in the relative group compared to the normal control group.

A recent meta-analysis of six studies involving relatives of individuals with schizophrenia and normal controls showed a small and non-significant effect size (Xu et al., 2011). In some studies (Ismail et al., 1998; Gourion et al., 2004; Ismail, 2000) MPAs correlated among patients and their relatives, possibly supporting a genetic influence, while in other reports MPAs were more common in sporadic than familial schizophrenia (Griffiths et al., 1998). Gourion et al. (2004) found that parents of individuals with schizophrenia had higher MPAs than controls, and that parents who were classified as presumed carriers (those who had at least one first-or second-degree relative with schizophrenia in their ascendant or collateral pedigree) showed a trend toward higher total MPA scores than presumed non-carriers (those with no family history of schizophrenia-related disorders other than in their offspring). Limitations of the studies included in the only published meta-analysis on the MPAs prevalence in relatives of patients (Xu et al., 2011) are that they did not report on body regions and individual items, and using the Waldrop Scale or the Modified Waldrop Scale,

they did not evaluate a differentiation of minor malformations and phenogenetic variants during the individual analysis.

First in literature, we report here on the analyses of MPAs among relatives of schizophrenia patients by the differentiation of minor malformations and phenogenetic variants, and emphasize that insults resulting abnormal brain development may appear both during and after the first and second trimester (only phenogenetic variants were more prevalent in the relative group, while one minor malformation was significantly more common among the relatives of patients). We see it as an important result, that relatives of schizophrenia patients showed a higher frequency of MPAs in the head and the mouth regions, and one minor malformation (flat forehead) was more common in this group of individuals. Previous findings suggested that anomalies of the head and the mouth may have more relevance to the hypothetical neurodevelopmental failure in schizophrenia patients (Green et al., 1989; Lane et al., 1997; Ismail, 1998; Trixler et al., 2001; Tényi et al., 2015; Tikka et al., 2015). Similar to our results, most recently Tikka et al. (2015) reported that MPAs in the craniofacial region were significantly higher in the first-degree relative group than the healthy control group. It might also be important, that minor physical anomalies at different localizations may represent different origins, as familial versus non-familial. Aksoy-Poyraz et al. (2011) reported on ear and limb anomalies, greater head circumference and intercanthal width, which showed a correlation between patients and their healthy siblings. Their results indicate that these anomalies might reflect a familial predisposition for schizophrenia (Aksoy-Poyraz et al., 2011). Similar correlations of MPAs between schizophrenia patients and relatives were reported at eyes, hands (Compton et al., 2007) and ears (Ismail et al., 2000; Compton et al., 2007).

Conclusion

Considering the endophenotype concept, it should be reminded that although MPAs are not specific to schizophrenia and are reported in other neurodevelopmental disorders (Compton et al., 2011), however our results and some previous reports on the more common appearance of these somatic markers in the relatives of schizophrenia patients can suggest these anomalies as endophenotypic traits, pointing at altered neurodevelopment as a core neurobiological deficit in schizophrenia.

II: Mentalizing impairment in patients with schizophrenia

Introduction

The term social cognition refers to the ability to perceive, understand and respond to the intentions, behaviours, and dispositions of others. The impairment of social cognitive functioning, and poor community functioning are frequently associated with schizophrenia (Frith et al, 1996; Priebe, 2007,Herold et al, 2002; Bora et al, 2009), In addition, strong association has been found between social cognition, functional outcome, and quality of life (Couture et al, 2006; Fett et al, 2011; Tas et al, 2013). Since appropriate social cognitive capacities are essential for the adequate functioning in human societies, the exploration of the underlying mechanisms for social cognitive deficits in schizophrenia seems to be essential. A better understanding of their background can open the way to find novel treatment approaches in the future.

Our recent fMRI study (Varga et al., 2013) examined the mentalization abilities and activation patterns during task solving of schizophrenic patients during remission. Using auditory stimuli we examined the different phases of irony understanding separately, and evaluated if the contextual information (verbal cue alluding to the emotional state of the speaker) affects the irony understanding performance, and the related activation patterns of the patients. In the study 21 schizophrenia patients were included (all of them in remission), compared to 24 healthy matched individuals.

According to the results the schizophrenia group performed significantly worse than the control group in the irony tasks. In addition the activation patterns observed during the interpretation of the task were notably different. In the context phase the patients showed significantly higher activations in the pars opercularis of the left inferior frontal gyrus and in the left inferior parietal lobule than the control group. In the irony part of the task the patients showed significantly lower activations than the healthy controls, and although the activation patterns of the patients did not represent mentalizing effort, the areas related to lingual and auditory representations showed activation. According to these results the functional brain anomalies underlying the irony comprehension in schizophrenia can be detected during the context and the ironic statement phase.

In our recent study (Varga et al., 2014) a group of schizophrenia patient with good intellectual qualities were examined. The general intelligence was measured by the Hungarian version of the Wechsler Adult Intelligence Scale, according to which the IQ of the patients was in the normal range, and the mean IQ of the patients did not differ significantly from that of the healthy control group. Our results showed that the patients performed similarly to the controls in the irony comprehension tasks. Because during solving other tests measuring mentalizing abilities the patients performed significantly worse than the controls, we assume that the patients were able to solve these tasks depending on their problem-solving capabilities, without having to use mentalization based strategies.

Aims of the study

Our aim was to examine –similar to our former study- the activation patterns of schizophrenia patients with good neurocognitive abilities during irony comprehension tasks. Our assumption was that the patients solve the tasks with a performance similar to the control group, but there are differences in the activation patterns of the two groups, as the patients do not activate the neuronal circuits responsible for mentalizing.

Methods

14 patients with schizophrenia and 14 healthy individuals as a control group were examined by fMRI scan. All the participants were right handed, which was assessed by the Edinburgh Handedness Inventory test (Oldfield, 1971). The general intelligence was measured by the Hungarian version of the Wechsler Adult Intelligence Scale (WAIS; (Wechsler, 2007)). THE Mean IQ score of the schizophrenia group was above 100, which did not differ significantly from the score of the control group (two sample t-test: $p=0.16$) (Table 4.). The patients were diagnosed according to the DSM-IV criteria. All patients were on maintenance antipsychotic medication. After complete description of the study to the participants, written informed consent was obtained. Ethical perspectives were established in accordance with the latest version of the Declaration of Helsinki.

Stimuli were presented with NordicNeuroLab fMRI Hardware (VisualSystem, AudioSystem,

ResponseGrip, SyncBox). During scanning, participants' responses were registered and saved; response accuracy was evaluated after scanning. Functional magnetic resonance (MR) imaging was performed on a 3T MR scanner (Siemens Magnetom Trio, Siemens AG, Erlangen, Germany) with 12-channel phased array TIM head coil for radio frequency reception. We used a standard EPI sequence to obtain functional MR images. We acquired 567 volumes per session. Anatomical images were acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence. The same tasks were used as in our above mentioned study (Varga et al., 2013). The irony and control tasks encased in short scenarios were matched in syntactic structure, semantic complexity and length.

The irony tasks consisted of a short context phase describing a social situation with two participants, this was followed by an „ironic statement", in which one of the participants made an ironic remark the literal meaning of which was the opposite of the intended one. The control tasks were short, descriptive, and based on physical causality, which entailed the representation of non-intentional causal links from the part of the participants (for example the wind shut the windows in the house. Because the passive objects did not move by themselves and did not react to humans, the answering of the task didn't need mentalizing activity. After each scenario the participants needed to answer a yes/no question by pressing an answer button. The length of each scenario across the different conditions and also the length of the different phases of the scenarios (context phase, statement phase and question–answer–phase) were strictly matched; hence there was no significant difference between the lengths of them.

For the presentation of the tasks we used an event-related design as in our former study (Varga et al., 2013). Each task started with a context phase (1), followed by a 2–4 s (jittered) inter-stimulus interval. The ironic statement phase (2) appeared next, and finally a comprehensive question (3) followed. Between tasks, inter-trial intervals of 5–7 s (jittered) were used. In order to simulate real social interactions -where ironic statements occur unexpectedly- the 30 tasks were presented to the participant in arandomly mixed sequence.

For the statistical analysis of the performance in the tasks the SPSS 20 package was used. To determine between-group differences two sample t-test and Mann-Whitney tests were used. Functional data sets were analysed using FSL 4.1.3. (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl). FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL. Blood oxygenation level-dependent

(BOLD) changes during the different phases of the tasks were modelled using separate regressors during context phase for Irony (I) and Control (C) conditions, during statement phase for I and C conditions; as well as during question–answer phase for I and C conditions. To find where the BOLD response to the ironic statement is greater than the BOLD response to the control statement, contrasts were defined of regressors: context phase: I > C, statement phase: I > C, question–answer phase: I > C. The I > C contrasts of regressors were defined in order to eliminate the confounding factor of basic semantic processing.

At first-level statistical analysis the mentioned contrasts were calculated separately for every participant. The resulting first-level contrast images were entered into higher level analyses to test for differences in activation within- and between study groups. In group analysis Z (Gaussianised T/F) statistic images were threshold using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

Results

No significant difference between the performances of the two groups was found (Mann-Whitney test: irony: p=0.5; control: p=0.155) (table 4.).

In the I>C contrast during the context phase the control group showed activations in the left inferior parietal lobule (IPL), the left precuneus and the left cuneus. The patients, on the other hand, showed extensive activations in many cortical and subcortical areas in both hemispheres. Significant between-groups differences were also registered in the context phase, the patients showed higher activations in the left medium frontal gyrus (MFG, BA 6), the left inferior parietal lobule and the whole left thalamus to the left parietal opercular region (anterior part of the supramarginal gyrus) and to the left Heschl's gyri. In the right hemisphere the MFG, the IPL and the right dorsolateral prefrontal cortex (DLPFC) showed significantly higher activation compared to the control group.

In the I>C contrast during the ironic statement the healthy controls activated the following areas (table 3.): the left superior frontal gyrus (SFG) to the dorsomedial prefrontal cortex (DMPFC) and to the paracingulum; the anterior region left middle temporal gyrus to the Broca region; the right superior temporal sulcus. The patients activated the posterior part of the left MTG to the posterior part of the superior temporal gyrus (which matches the Wernicke Area); the homologous parts in the right hemisphere and the left temporal pole to

the Broca area (table 2). There were no significant between-groups differences in the irony phase.

In the I>C contrast neither group showed significant activations during the question/answer phase.

Because substantial differences were registered between the activations of the two groups – regardless of both performing similarly well in the tasks- we examined if the patients significantly higher activations may be due to deactivation deficits. To test this assumption the deactivation patterns in both groups during the context phase were examined. According to the results, while the healthy controls showed extensive deactivations in the left and right IPL, at the left medial frontal gyrus (premotor area, BA 6), and the left planum temporale (figure 1.), no deactivations were detectable in the patient (table 5.).

Discussion

According to our current study – similar to our recent results – in a group of schizophrenia patients showing good neurocognitive abilities the subjects performed similar to the control group during irony comprehension tasks. Despite the performance of the schizophrenia group during the irony task was similar to that of the control group, the activation patterns observed were significantly different. To understand the cause of these differences deactivation patterns were examined in both groups during the context phase. The results showed that while healthy controls showed wide-spread deactivation patterns, the patient group showed no deactivations.

The control group showed the activation of neuronal circuits correspondent to our former studies. In the context phase the results showed the activation of the left temporo-parietal junction – showing the recognition of communication intent (Saxe and Wexler, 2005; Walter et al., 2014), and the procession of complex social situations (Wible, 2012), while the precuneus plays a role in the self-reflective mechanisms and autobiographic memory processes. The temporo-occipital areas take part in the higher level integration of linguistic information, which function is supported by the ventral occipital areas (cuneus). During the ironic statement phase the healthy group activated the regions known to be connected to the mentalizing functions. Amongst these the most important – according to recent literature – are the prefrontal-paracingular structures (Brunet-Gouet and Decety, 2006.).

In contrast to the healthy group the patients showed activations not only in the temporo-parietal junctions and precuneus, but an expansive activation network was observed including prefrontal, temporo-parietal and subcortical areas. In the same phase the between-group comparison showed significantly higher activations of the left and right premotor cortex, the left and right IPL in the patient group. Both are known to be mirror neuron areas (Molenberghs et al., 2012; Rizzolatti and Craighero, 2004.), which may play a role in the understanding of texts including human interactions. Besides these further activations were found at the areas of the Heschl's gyrus and the IPL playing a role in processing auditory information.

In addition the DLPFC, the region responsible for working memory and episodic memory functions (Gilbert et al., 2006) was activated. These results mean that the patient draw on the mirror neuron areas, and the regions connected with text comprehension and memory functions more than the healthy controls.

In the ironic statement phase the patients did not activate the areas described to be connected to mentalizing efforts, despite being able to solve the tasks. Our results showed that instead of the regions responsible for mentalization (like the DMPFC/paracingulum, STS seen in the healthy group) the patients mobilized the domain general regions responsible for text comprehension. The latter result supports our theory, that the patients with good cognitive capacities are able to solve the irony tasks, but instead of using mentalization based mechanism, they utilize non mentalization based compensation mechanisms.

Because during the context phase significantly higher activations were measured in the patient group in the ambilateral frontal, parietal, and the left temporal regions, we examined if this expansive hyperactivity patterns could be due to a deactivation deficit. Deactivated regions are regions in which higher BOLD response is measured during tasks meaning lesser cognitive strain, or in rest period, than in the targeted tasks. (Buckner et al., 2008).

We found that while the healthy group deactivated the regions of the so called default mode network (DMN) during the context phase, the patients did not show deactivation in any regions. Based upon these results, we assume that the differences found in the context phase may be due to the patient group not activating the DMN significantly stronger in the tasks needing less effort, as it is seen in the control group. The „default mode network" is active when the person is not sleeping, but is either not paying attention to the surrounding world, is musing, brooding or just is resting relaxed. During goal oriented activity -like solving tasks-

the DMN deactivates (task induced deactivation), and the network needed to solve the task is activated instead. Multiple studies concerning patients having different activation patterns than healthy controls can be found (summarized by Pomarol-Clotet et al., 2008). These studies found deactivation deficits in different regions, including the DMN, and the deactivation anomalies showed connection with poorer performance in different cognitive tasks. Because DMN basically plays an important role in self-reference, it's abnormal functioning may not only play a role in the cognitive deficits of schizophrenia, but in the development of the symptoms as well.

Summarizing our results we find that patients with schizophrenia do not solve irony tasks by mentalization. It may be possible that the mentalization deficits of schizophrenia patients – which are by some theories result of ineffective processing of information in the context – may be due to the inability to deactivate the DMN during the processing of the social situation/context.

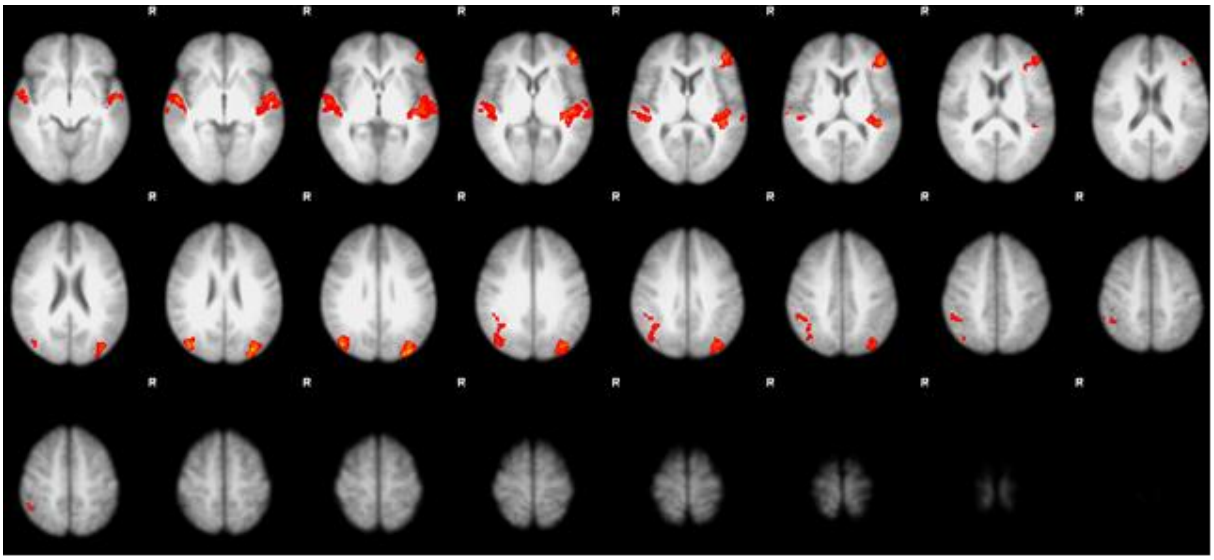

Figure 1.: In the I>C contrast, during the processing of context phase, the following areas showed deactivations in the control group: Left planum temporale, left medial temporal gyrus, right inferior parietal lobule, right superior occipital gyrus, and left medial frontal gyrus. In group analysis Z (Gaussianised T/F) statistic images were threshold using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

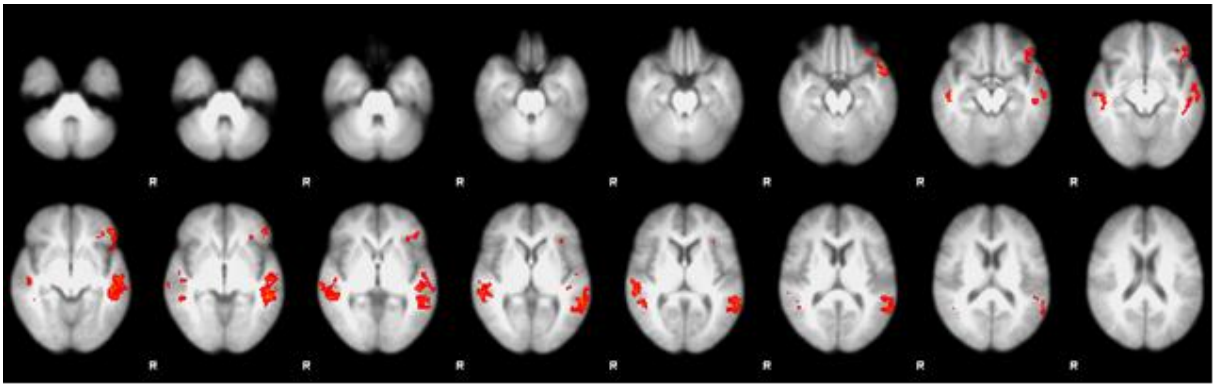

Figure 2: In the I>C contrast, during the processing ironic statement, the following areas showed activations in the patient group: right and left medial temporal gyrus, left temporal pole. In group analysis Z (Gaussianised T/F) statistic images were threshold using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

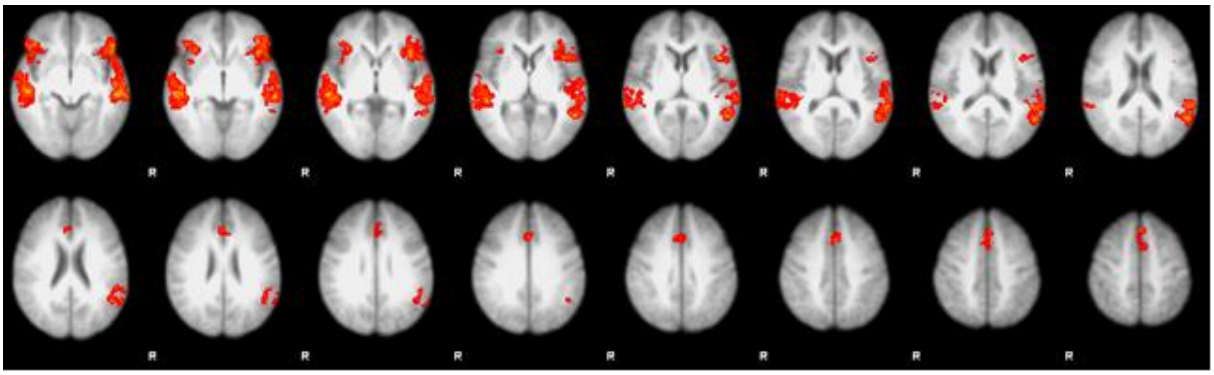

Figure 3: In the I>C contrast, during the processing ironic statement, the following areas showed activations in the control group: left medial temporal gyrus, right superior temporal sulcus and the midline dorsomedial prefrontal cortex. In group analysis Z (Gaussianised T/F) statistic images were threshold using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$.

Table 4: Demographical data and performance in irony tasks of the control and patient group

Variables	Control group (n=14)	Patient group (n=14)[a]	p value
	% Mean±deviation (range)	% Mean±deviation (range)	
Gender (% female)	57,14	57,14	
Handedness (% right)	100	100	
Age (years)	33.43+-6.7 (25-55)	38.00+-7.55 (31-55)	0.14[b,c]
IQ (MAWI)	115.86+-6.36 (105-125)	113.43+-7.6 (100-127)	0.16[b,c]
PANSS (Positive and Negative Symptom Scale) total		66.57+-13.83 (33-91)	
PANSS positive		14.48+-3.93 (7-24)	
PANSS negative		17.61+-6.1 (8-27)	
PANSS depression subscale		9.05+-2.99 (4-15)	
PANSS general		34.48+-7.3 (18-46)	
Duration of illness (years)		11.95+-8.45 (1-31)	
Onset of illness (year)		26.76+-6.06 (17-39)	
Irony tasks	14.15+-1.37 (10-15)	13.43+-1.33 (11-15)	0.5[b,c]
Control tasks	14.77+-0.43 (14-15)	14.36+-0.78 (13-15)	0.155[b,c]

a Diagnosis of schizophrenia according to DSM-IV (n = 14).

b For in between group comparison Mann-Whitney test was used

c Statistically significant difference $p < 0.05$, uncorrected.

Regions (BA)	Hem	x	y	z	Zmax	Voxel	Hem	x	y	z	Zmax	Voxel	Hem	x	y	z	Zmax	Voxel
	Control group						**Patient group**						**Patient group > Control group**					
Activations during the context phase of tasks																		
Temporoparietal junction (39)	L	−56	−52	20	4.52	555												
Cuneus (18)	R	20	−90	20	3.36	493												
Precuneus (7)		0	−60	30	3.51	441												
Temporoparietal junction (39)							L	−60	−52	10	5.72	18361						
Superior parietal lobule							*L*	*−42*	*−36*	*48*	*5.66*							
Medial frontal gyrus (6)							*L*	*−44*	*8*	*34*	*5.27*							
Insula (13)							*L*	*−30*	*26*	*−2*	*5.11*							
Anterior medial temporal gyrus div.							R	52	−24	−14	5.63	969						
Dorsolateral prefrontal cortex							R	40	46	26	4.14	830						
Thalamus							R	8	18	−8	3.75	568						
medial frontal gyrus (6)													L	−44	10	34	5.03	2278
Inferior parietal lobule (39)													L	−32	−72	36	4.14	2124
Medial frontal gyrus													R	44	10	32	5.44	1497
Inferior parietal lobule (39)													R	42	−46	46	4.67	1476
Thalamus													L	−22	−4	10	3.6	717
Dorsolateral prefrontal cortex													R	46	42	24	3.29	441
Deactivations during the context phase of tasks																		
Planum temporale	L	−42	−34	8	4.34	1117												
Medial temporal gyrus	R	60	0	−20	4.31	718												
Inferior parietal lobule	R	44	−74	32	4.4	631												
Superior occipital gyrus	L	−34	−84	30	5.03	626												
Medial frontal gyrus	L	−50	46	2	4.57	504												
Activations during the ironic statement phase of tasks																		
Medial temporal gyrus	L	−54	0	−20	5.08	5136												
Superior temporal sulcus	R	50	−22	−6	5.47	3316												
Dorsomedial prefrontal cortex		0	28	52	3.84	787												
Medial temporal gyrus							L	−52	−40	−4	4.08	1311						
Medial temporal gyrus							R	58	−38	2	3.79	622						
Temporal pole							L	−50	12	−22	4.21	466						

Table 5. Significant activations during the context and ironic statement phases of the tasks in the control and patient group. During the processing of context phase significant activation differences were found.

X, y, z coordinates in mm., in Montreal Neurological Institute (MNI) system.

In the table local maximas were used. In group analysis Z (Gaussianised T/F) statistic images were threshold using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$.

BA Brodmann area; L left, R right, Hem hemisphere, Voxel number of voxels

Summary of new observations

- First in literature, we report on the analysis of MPAs by the differentiation of minor malformations and phenogenetic variants among relatives of schizophrenia patients.
- We found that relatives of schizophrenia patients showed a higher frequency of MPAs in the head and the mouth regions, which result - according to the recent literature – may refer with higher probability to the neurodevelopmental failures playing a role in the etiology of schizophrenia
- One minor malformation (flat forehead) was more common among the healthy relatives of schizophrenia patients.
- Our results support the endophenotypic trait of MPA-s, referring to an altered brain development as a relevant neurobiological factor in the background of schizophrenia.
- In our second study we described that schizophrenia patients with good neurocognitive capacities may solve irony task not by mentalization mechanisms, but by so called non-mentalization bases compensation strategies.
- Based on our results we may assume that the mentalization deficits found in patients with schizophrenia maybe due to the inability to deactivate the DMN during the processing of contextual information.

Publications

A. Publications related to the thesis:

Tényi T., Hajnal A., Halmai T., Herold R., Simon M.,Trixler D., Varga E.,Fekete S., Csábi Gy. /2014/: Minor fizikális anomáliák szkizofrén betegek hozzátartozói között. Szisztematikus áttekintő közlemény. **Psychiatria Hungarica**, 29,208-213.

Hajnal A., Tényi T.,Varga E., Simon M., Halmai T., Németh N., Fekete S., Trixler D., Herold R. /2014/: Szociális kognitív eltérések szkizofrén páciensek első fokú hozzátartozói között. Szisztematikus áttekintő közlemény. **Psychiatria Hungarica**, 29, 301-307.

Tényi T., Hajnal A., Csábi Gy. /2015/ : The Importance of Research on the Relatives of Schizophrenia Patients – Towards Endophenotypic Markers. **International Journal of Emergency Mental Health and Human Resilience**, 17,No 2, 545.

Hajnal A., Csábi Gy., Herold R., Jeges S., Halmai T., Trixler D., Simon M., Tóth Á.L., Tényi T. /2016/: Minor physical anomalies are more common among the first-degree unaffected relatives of schizophrenia patients – Results with the Méhes Scale. **Psychiatry Research,** 2016 Mar 30;237:224-8., **IF: 2,467**

Varga E.,Herold R., Schnell Zs.,Simon M.,Hajnal A., Járai R., Fekete S.,Tényi T./2015/ : Jó általános kognitív készségek hatása az irónia megértésére szkizofréniában. Funkcionális MRI vizsgálat**. Psychiatria Hungarica,** 30, 308-317.

Varga E., Simon M., Tényi T.,Schnell Zs., Hajnal A., Orsi G.,Dóczi T.,Komoly S.,Janszky J.,Füredi R.,Hamvas E.,Fekete S., Herold R./2013/: Irony comprehension and context processing in schizophrenia during remission – A functional MRI study. **Brain and Language**, 126,231-242. **IF: 3,309**

Varga E., Schnell Zs., Tényi T., Németh N., Simon M., Hajnal A., Horváth R.A., Hamvas E., Járai R., Fekete S., Herold R. /2014/ : Compensatory effect of general cognitive skills on non-

literal language processing in schizophrenia : A preliminary study. **Journal of Neurolinguistics,** 29, 1-16. **IF: 1,489**

Herold R., Varga E., Mike A., Tényi T., Simon M., Hajnal A., Fekete S., Illés Zs./2015/: Mentalizációs deficit neurológiai betegségekben: összefoglaló közlemény. **Ideggyógyászati Szemle**, 68, 364-373. **IF: 0,386**

Schnell Zs., Varga E., Tényi T., Simon M., Hajnal A., Járai R., Herold R. /2016/: Neuropragmatics and irony processing in schizophrenia – Possible neural correlates of the meta-module of pragmatic construction**. Journal of Pragmatics**, 92, 74-99. **IF: 0,831**

Varga E., Herold R., Schnell Zs., Horváth R., Simon M., Hajnal A., Tényi T. /2016/ : The processing of humour by individuals suffering from schizophrenia. **European Journal of Humour Research**, 4, 102-121.

Impact Factor: 8,482

B. Abstracts related to the thesis:

Varga E., Simon M., Hajnal A., Tényi T., Fekete S., Herold R.. / 2009 / : A magasabb szintű mentalizációs készségek deficitje szkizofréniában. **Psychiatria Hungarica**, 23, Suppl., 158.

Herold R.,Varga E.,Hajnal A.,Orsi G.,Tényi T., Fekete S., Simon M. /2009/ : A mentalizációhoz kötődő nyelvi kontextus hatása az agyi funkcionalitásra szkizofréniában. Psychiatria Hungarica, 24,Suppl., 79.

Varga E., Hajnal A., Schnell Z., Orsi G., Tényi T., Fekete S., Simon M., Herold R./ 2010/: Exploration of irony appreaciation in schizophrenia : a functional MRI study. **European Psychiatry**, 25,Suppl. 1, Abstracts on CD-ROM. PW01-156. **IF: 3,365**

Varga E.,Hajnal A., Tényi T., Fekete S.,Simon M., Herold R./2010/ : The evaluation of mentalisation deficit with false-irony test in schizophrenia. . **European Psychiatry**, 25,Suppl. 1, Abstracts on CD-ROM. PW01-195. **IF: 3,365**

Varga E., Schnell Zs., Simon M., Hajnal A.,Tényi T., Fekete S., Herold R. /2010/ : Szkizofrén betegek irónia értésének vizsgálata fMRI-vel **Psychiatria Hungarica**, 25, Suppl. 142.

Varga E., Schnell Zs.,Simon M.,Hajnal A.,Tényi T., Fekete S., Herold R./2011/: Exploration of irony comprehension in schizophrenia with fMRI. **European Psychiatry**,26, Suppl. 1., Abstracts on CD-ROM. P02-36 **IF: 2,776**

Simon M.,Varga E., Hajnal A., Orsi G., Tényi T., Fekete S., Herold R. /2011/: Irony comprehension in bipolar disorder and schizophrenia: a functional MRI study. . **European Neuropsychopharmacology**, 21, Suppl. 3.,S310. **IF: 4,046**

Simon M.,Varga E., Hajnal A.,Orsi G.,Schnell Zs.,Tényi T., Fekete S.,Herold R./2011/:Az iróniaértés eltérései szkizofréniában és bipoláris zavarban – fMRI vizsgálat. **Psychiatria Hungarica,**26, Suppl., 112.

Varga E., Schnell Zs., Tényi T., Simon M., Hajnal A., Németh N., Herold R./2013/ : Impaired decoding of the flouting of the gricean maxims among schizophrenia patients. **European Psychiatry**, 28, Suppl. 1, Article 1552 **IF: 3,210**

Simon M., Varga E., Hajnal A., Orsi G., Herold R., Fekete S., Tényi T. /2014/ : Neural substrates of irony comprehension: are there any gender differences? **European Neuropsychopharmacology**, 24, Suppl. 2., S314-S315. **IF: 4,369**

Tényi T., Hajnal A., Halmai T.,Simon M., Varga E., Herold R., Csábi Gy./2015/: Endophenotypic Markers in the Relatives of Schizophrenia Patients:Systematic Reviews of Theory of Mind and Informative Morphogenetic Variant Studies. **European Psychiatry**, Abstract on USB, Article 0909. **IF: 3,439**

Hajnal A., Csábi Gy., Herold R., Jeges S., Halmai T., Trixler D., Simon M., Tóth Á.L., Tényi T. /2016/: Minor fizikális anomáliák gyakoribb előfordulása szkizofrén páciensek egészséges elsőfokú hozzátartozóiban – Eredmények a Méhes-skálával. **Psychiatria Hungarica,** Suppl. 1., 64.

Impact Factor: 24,57

C. Further publications:

Seress L, Ábrahám H, Hajnal A, Lin H, Totterdell S. /2005/: NOS-positive local circuit neurons are exclusively axo-dendritic cells both in the neo- and archi-cortex of the rat brain. **Brain Res.** 2005 Sep 21;1056(2):183-90. **IF: 2,840**

Simon M., Varga E., Hajnal A., Schnell Zs., Tényi T., Fekete S., Herold R./2011/: Theory of mind deficits of euthymic patients with bipolar I. disorder. Theoretical background and guidelines for neuroimaging research. **Psychiatria Hungarica**,26,178-187.

Mike A, Strammer E, Aradi M, Orsi G, Perlaki G, Hajnal A, Sandor J, Banati 2, Illes E, Zaitsev A, Herold R, Guttmann CR, Illes Z /2013/ : Disconnection mechanism and regional cortical atrophy contribute to impaired processing of facial expressions and theory of mind in multiple sclerosis: a structural MRI study. **PLoS One**. 2013 Dec 13;8(12):e82422. **IF: 3,230**

Impact factor: 6,070

D. Further abstracts:

Hajnal A., Herold R., Tényi T., Fekete S., Simon M. / 2008 / : Euthym bipoláris betegek mentalizációs teljesítményének vizsgálata : előzetes adatok. **Psychiatria Hungarica**, 23, Suppl. 63

Hajnal A., Herold R., Tényi T., Fekete S., Simon M. /2009/ : Euthym bipoláris betegek mentalizációs teljesítményének vizsgálata. **Neuropsychopharmacologia Hungarica**, 11, Suppl. 3, 20.

Hajnal A., Herold R., Varga E.,Tényi T.,Fekete S., Simon M. /2009/ : Euthym bipoláris betegek mentalizációs teljesítményének vizsgálata**. Psychiatria Hungarica**, 24, Suppl.,70

Simon M.,Varga E.,Hajnal A.,Orsi G.,Tényi T.,Fekete S., Herold R./2010/ : Brain activation during irony tasks in euthymic bipolar patients – a functional MRI study of social cognition. **European Psychiatry**, 25,Suppl. 1, Abstracts on CD-ROM. PW01-154. **IF: 3,365**

Hajnal A., Varga E., Herold R., Tényi T., Fekete S., Simon M./2010/ : Euthymic bipolar patients' deficits in social cognition tasks. **European Psychiatry**, 25,Suppl. 1, Abstracts on CD-ROM. P01-44. **IF: 3,365**

Halász J, Hajnal A, Szabó Zs, Osváth P, Kovács K, Gádoros J, Fekete S, Vörös V /2010/ : HPA-tengely működésének és a neurokognitív funkciók asszociációjának vizsgálata violens szuicid kísérleten átesett személyekben **Psychiatria Hungarica,** 25, (Suppl) p. 55. (2010)

Simon M., Varga E., Hajnal A.S., Orsi G., Tényi T., Fekete S., Herold R. /2010/ : Irony comprehension in bipolar disorder: an fMRI study. **European Neuropsychopharmacology**, 20, Suppl. 3., S295. **IF: 4,201**

Hajnal A.,Varga E.,Schnell Zs.,Orsi G., Tényi T., Fekete S., Simon M./2010/ : Az irónia megértése bipoláris zavarban – 3T funkcionális MR vizsgálat. **Psychiatria Hungarica**,25, Suppl. 115

Vörös V, Halász J, Osváth P, Szabó Z, Hajnal A, Kovács K, Vörös O, Gádoros J, Fekete S /2011/ : Neurocognitive dysfunctions and testassociated cortisol levels in patients with suicidal behaviour. **European Neuropsychopharmacology**,21, Suppl. 3, S443 **IF: 4,046**

Simon M., Herold R., Hajnal A., Varga E., Fekete S., Tényi T. /2013/ : Theory of mind deficit in bipolar patients with subsyndromal illness. **European Neuropsychopharmacology**, 23, Suppl. 2., S295-S296. **IF : 5,395**

Impact factor: 20,372

Ackonwledgements

I would like to express my gratitude to Prof. Dr. Tamás Tényi, head of the Psyschiatry Programme of the Clinical Neuroscience Doctoral School and my thesis supervisor, for the vast support, help and motivation.

I am grateful to Prof. Dr. Sámuel Komoly, Head of the Clinical Neuroscience Doctoral School. I express my thanks to Prof.Dr. Sándor Fekete for supporting my PhD studies, my collegaues Dr. Róbert Herold, Dr. Mária Simon and és Dr. Eszter Varga for their valuable help and professional support.

Last but not least, I thank my family, for all their support throughout my studies and work, without their love and encouragement this thesis would not have been completed.

The studies were supported by the Hungarian Brain Research Program, Grant No.: KTIA – 13 - NAP-A-II/12.